IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Patent Application No. 10/579,988

Confirmation No. 4910

Applicant: Leonard et al.

Filed: August 8, 2006

TC/AU: 1633

Examiner: Maria Gomez Leavitt

Docket No.: 252024 (Client Reference No. E-120-2003/1-US-05)

Customer No.: 45733

APPELLANTS' APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In support of the appeal from the final rejection dated July 14, 2010, Appellants now submit their Brief.

Real Party In Interest

The patent application that is the subject of this appeal is assigned to the Government of the United States of America, Represented by the Secretary, Department of Health and Human Services.

Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal.

Status of Claims

Claims 5, 8, 10-12, 18, 20, and 32-35 are currently pending and are the subject of this appeal. Claims 1-4 were canceled in the "Preliminary Amendment" dated May 19, 2006. Claims 6-9, 13-17, and 21-31 were canceled in the "Reply to Office Action" dated January 17, 2008. The pending claims are reproduced in the "Claims Appendix" attached hereto.

Status of Amendments

The amendments to claims 5 and 18 set forth in the "Reply to Office Action" dated April 29, 2010, have been entered as indicated by the Office Action dated July 14, 2010. .

Summary of Claimed Subject Matter

Claims 5 and 18 are the only independent claims. Independent claim 5 is directed to a method for enhancing an immune response in a subject. The method comprises (a) isolating a population of cells comprising one or more of a mature B cell and a B cell progenitor from the subject; (b) contacting the population of cells comprising one or more of a mature B cell and a B cell progenitor with a composition comprising (i) an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid sequence of SEQ ID NO: 1, wherein the variant comprises the amino acid sequence of SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions, and wherein the variant retains the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor, wherein the population of cells optionally is contacted with at least one antigen, and wherein the composition induces differentiation of at least one of the mature B cell and the B cell progenitor into one or more of a memory B cell and a plasma cell; (c) isolating or purifying one or more of the memory B cell and the plasma cell; and (d) introducing at least one of the memory B cell and the plasma cell into the subject, thereby enhancing the immune response (as supported by page 2, line 30, through page 3, line 3; page 8, lines 6-13; page 9, lines 29-31; page 20, lines 8-19; page 29, lines 21-26; page 31, lines 14-27; and page 34, line 31, through page 35, line 3).

Claim 8 depends from claim 5 and recites that the subject is a human subject (as supported by page 9, lines 7-8). Claims 10 and 11 depend directly or indirectly from claim 5, respectively, and recite that the population of cells is contacted with at least one composition comprising an antigen and that the antigen comprises a viral antigen, a bacterial antigen, or an antigen from a parasite (as supported by page 9, lines 29-31; and page 34, line 31, through page 35, line 1). Claim 12 depends from claim 5 and recites that the B cell progenitor is an immature B cell (as supported by page 9, lines 26-27). Claim 32 depends from claim 5 and recites that the composition comprises (i) the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 (as supported by page 29, lines 21-26). Claim 34 depends from

claim 5 and recites that the composition comprises (ii) the variant of the amino acid sequence of SEQ ID NO: 1, wherein 1-5 amino acids of SEQ ID NO: 1 have been substituted, deleted, or added (as supported by page 31, lines 14-27).

Independent claim 18 is directed to a method for treating a subject with a condition comprising a specific deficiency of at least one of memory B cells and plasma cells. The method comprises (a) isolating a population of cells comprising one or more of a mature B cell and a B cell progenitor from the subject; (b) contacting the population of cells comprising at least one of a mature B cell and a B cell progenitor *ex vivo* with a composition comprising (i) an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid SEQ ID NO: 1, wherein the variant comprises the amino acid sequence of SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions, and wherein the variant retains the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor, wherein the population of cells optionally is contacted with at least one antigen, and wherein the composition induces differentiation of at least one B cell into one or more of a memory B cell and a plasma cell; (c) isolating the memory B cell, the plasma cell, or both; and (d) introducing at least one of the memory B cell and the plasma cell into the subject (as supported by page 3, lines 4-9; page 8, lines 6-13; page 9, lines 29-31; page 10, lines 1-16; page 20, lines 8-19; page 29, lines 21-26; page 31, lines 14-27; and page 34, line 31, through page 35, line 3).

Claim 20 depends from claim 18 and recites that the subject is a human subject (as supported by page 9, lines 7-8). Claim 33 depends from claim 18 and recites that the composition comprises (i) the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 (as supported by page 29, lines 21-26). Claim 35 depends from claim 18 and recites that the composition comprises (ii) the variant of the amino acid sequence of SEQ ID NO: 1, wherein 1-5 amino acids of SEQ ID NO: 1 have been substituted, deleted, or added (as supported by page 31, lines 14-27).

Grounds of Rejection to be Reviewed on Appeal

Whether claims 5, 8, 10-12, 18, 20, and 32-35 are unpatentable under 35 U.S.C. § 103(a) over Newell et al. (U.S. Patent Application Publication 2003/0138433) and Novak et al. (U.S. Patent Application Publication 2003/0125524).

Argument

A patent claim is invalid if, at the time the invention was made, the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (a) the scope and content of the prior art, (b) the level of ordinary skill in the prior art, (c) the differences between the claimed invention and the prior art, and (d) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

Appellants submit that the Examiner has erred in determining that the invention was *prima facie* obvious. The subject matter of claims 5, 8, 10-12, 18, 20, and 32-35 is unobvious as is apparent from a discussion of the four *Graham* factors.

a. The Scope and Content of the Prior Art

The Newell reference discloses a method for promoting antigen-specific immune responses comprising obtaining B cells that were isolated from a subject and contacting the B cells *in vitro* with a target antigen-conjugate to produce target antigen-conjugate manipulated cells, and infusing the target antigen-conjugate manipulated cells into the subject (see paragraph 0015). The target antigen conjugate comprises a target antigen that elicits a Th2 response conjugated to an antibody, a fragment of an antibody, a peptide, and/or a molecule that selectively binds a B cell cell-surface immunoglobulin (see paragraph 0015). The Newell reference discloses that the *in vitro* contacting of the isolated B cells with a target antigen-conjugate further can comprise contacting the isolated B cell with a B cell costimulating agent (e.g., TSA-1, CD2, CD5, CD24, CD28, CD40L, CD49a, CD80, CD81, and/or CD86) or a Th2 cytokine (e.g., IL-4, IL-5, IL-6, IL-9, IL-10 and/or IL-13) (see paragraph 0015).

The Novak reference discloses the amino acid sequence of zalpha11 ligand (i.e., IL-21) (see Figure 1). The Novak reference discloses a method of stimulating an immune response in a mammal exposed to an antigen or pathogen (e.g., B cell tumor, virus, parasite, or bacterium) comprising administering zalpha11 ligand to the subject (see paragraph 0164). The Novak reference additionally discloses that zalpha11 ligand polypeptides are useful for

stimulating proliferation, activation, differentiation, induction, or inhibition of specialized cell functions of epithelial cells and cells of the hematopoietic lineages, such as T cells, B cells, NK cells, dendritic cells, monocytes, and macrophages (see paragraph 0125).

b. Level of Ordinary Skill in the Art

While no findings were made during prosecution concerning the level of ordinary skill in the art, the level of ordinary skill in the art can be considered to be relatively high, such that one of ordinary skill in the art can be considered to be a person with an advanced degree and several years of experience in the field of immunology.

c. Differences Between Claimed Invention and Prior Art

The present invention, as defined by appealed claims 5, 8, 10-12, 32, and 34, is directed to a method for enhancing an immune response in a subject comprising (a) isolating a population of cells comprising one or more of a mature B cell and a B cell progenitor from the subject; (b) contacting the population of cells comprising one or more of a mature B cell and a B cell progenitor with a composition comprising (i) an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid sequence of SEQ ID NO: 1, wherein the variant comprises the amino acid sequence of SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions, and wherein the variant retains the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor, wherein the population of cells optionally is contacted with at least one antigen, and wherein the composition induces differentiation of at least one of the mature B cell and the B cell progenitor into one or more of a memory B cell and a plasma cell; (c) isolating or purifying one or more of the memory B cell and the plasma cell; and (d) introducing at least one of the memory B cell and the plasma cell into the subject, thereby enhancing the immune response. Additionally, the present invention, as defined by appealed claims 18, 20, 33, and 35, is directed to a method for treating a subject with a condition comprising a specific deficiency of at least one of memory B cells and plasma cells, wherein the contacting of the population of cells in (b) of the above-described method is done *ex vivo*.

The disclosures of the Newell and Novak references, when considered alone or in combination, differ from the subject matter of the appealed claims for the following reasons.

1. No reason provided to substitute zalpha ligand for a Th2 cytokine

In the Office Action dated July 14, 2010, the Examiner contends that the Newell reference discloses a method for promoting antigen-specific immune responses by obtaining B cells isolated from a subject, wherein the B cells have been contacted *in vitro* with a target antigen-conjugate to produce target antigen-manipulated B cells (see page 4, last paragraph). In the Office Action dated January 4, 2010, the Examiner acknowledges that the Newell reference does not teach contacting a population of mature B cells or a B cell progenitor with IL-21 (see page 6, lines 4-5). Indeed, IL-21 is not mentioned in the Newell reference. However, in the Office Action dated July 14, 2010, the Examiner contends that the Newell reference discloses contacting isolated B cells with cytokines (e.g., IL-2, TNF-α, IFN-γ, IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13), which the Examiner contends provides optimal help for humoral immune responses, such as IgE and IgG4 antibody isotype switching, promotes high level antibody production, promotes cell growth, and induces viral resistance (see page 4, last paragraph). Therefore, the Examiner contends that it would be obvious for one of ordinary skill in the art to substitute the cytokine of zalpha ligand (i.e., IL-21) from the Novak reference for the cytokines disclosed in the Newell reference in order to arrive at the invention of the appealed claims.

Appellants note that the Newell reference discloses that the isolated B cells can be contacted *in vitro* with a target antigen-conjugate and a Th2 cytokine (see paragraph 0015 at page 2, column 1, last four lines, and paragraph 0065). As examples of the Th2 cytokine, the Newell reference discloses IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 (see paragraph 0015 at page 2, column 2, lines 4-5, and paragraph 0065). Therefore, the Newell reference does not teach or suggest contacting the isolated B cells with *any* cytokine as indicated by the Examiner, but only teaches contact with a particular type of cytokine--a Th2 cytokine. In contrast, as disclosed by the specification, IL-21 (i.e., zalpha ligand) is a Th1 cytokine (see page 1, line 20) and *not* a Th2 cytokine.

The Newell reference differentiates between Th1 and Th2 responses and the cytokines produced by Th1 and Th2 responses. In particular, the Newell reference discloses that a number of lymphokines are produced by Th2 cells during a Th2 response, which include IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 (see paragraph 0009). These lymphokines of the Th2 response are involved in humoral responses, such as IgE and IgG4 antibody isotype switching (see paragraph 0009). On the other hand, the Newell reference discloses that IL-2, TNF-α,

IFN-γ, and lymphotoxin production are involved in a Th1 response (see paragraph 0009). Th1 cells are responsible for delayed type hypersensitivity and/or inflammatory responses (see paragraph 0009).

Since the Newell reference clearly describes that the isolated B cells can be contacted *in vitro* with a *Th2* cytokine, and differentiates between the Th1 and Th2 cytokines, as well as Th1 and Th2 responses, there would be no reason why one of ordinary skill in the art would substitute a Th1 cytokine, such as IL-21, for a Th2 cytokine in the method of the Newell reference.

As further evidence that one of ordinary skill in the art would have no reason to substitute IL-21 for a Th2 cytokine, such as IL-4 or IL-13, Appellants note that IL-21 opposes a major action that is Th2-mediated (immunoglobulin E production). In particular, Ozaki et al. (*Science, 298*: 1630-1634 (2002); cited as Reference BB in the Information Disclosure Statement filed May 16, 2006) discloses that IL-21 receptor knock-out mice have increased immunoglobulin E (IgE), which means that IL-21 decreases IgE, and Suto et al. (*Blood, 100(13)*: 4565-4573 (2002); cited as Reference BF in the Information Disclosure Statement filed May 16, 2006) discloses that IL-21 prevents antigen-induced IgE production by inhibiting germ line Cε transcription of IL-4-stimulated B cells.

2. No teaching of IL-21's ability to induce differentiation of B cells

Furthermore, neither the Newell reference nor the Novak reference discloses that IL-21 induces differentiation of human B cells into plasma cells and memory B cells, as required by the appealed claims. The Novak reference discloses that zalpha11 ligand (IL-21) stimulates the proliferation of B cells (i.e., increasing the population of undifferentiated B cells) in response to activating stimuli (see Example 44); however, the Novak reference does not provide any evidence that contacting IL-21 with a population of mature B cells and/or B cell progenitors results in the differentiation of the mature B cells and/or B cell progenitors into memory B cells and/or plasma cells, as required by the appealed claims (see paragraphs 6 and 8 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D.," which was submitted with the "Reply to Office Action" dated April 29, 2010). The Novak reference merely mentions that "[p]roteins of the present invention are useful for stimulating proliferation, activation, differentiation and/or induction or inhibition of specialized cell function of cells of the involved homeostasis of the hematopoiesis and immune function,"

wherein hematopoietic lineages include, but are not limited to, T cells, B cells, NK cells, dendritic cells, monocytes, macrophages, and epithelial cells (see paragraph 7 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D."). Thus, one of ordinary skill in the art, upon reading the Novak reference, would not have recognized that that contacting isolated mature B cells and/or B cell progenitors with IL-21 would induce differentiation of the B cells into plasma cells and memory B cells.

As acknowledged by the Examiner, the Newell reference does not mention IL-21, let alone the ability of IL-21 to induce differentiation of mature B cells and/or B cell progenitors into one memory B cells and/or plasma cells (see paragraph 9 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D."). The Newell reference merely discloses that a primary encounter with an antigen can stimulate specific B cells to differentiate into cells that produce antibody at a high rate (plasma cells) and populations of memory cells (see paragraph 9 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D."). Thus, based on the disclosure of the Newell reference, one of ordinary skill in the art would not have recognized that contacting isolated mature B cells and/or B cell progenitors with a composition comprising IL-21 would induce differentiation of the B cells into plasma cells and memory B cells.

3. No teaching of isolating memory B cell and/or plasma cell

Additionally, neither the Newell reference nor the Novak reference discloses isolating or purifying one or more of the memory B cell and the plasma cell (whose differentiation was induced by contacting mature B cells and/or B cell progenitors with IL-21) and introducing at least one of the memory B cell and the plasma cell into the subject, as required by the appealed claims.

d. Objective Evidence of Non-Obviousness

For purposes of the analysis here, there is no need to consider any objective criteria of nonobviousness. However, Appellants note that the invention is predicated on the inventors' discovery that contacting a population of cells comprising one or more of a mature B cell and a B cell progenitor with a composition comprising IL-21 induces differentiation of the mature B cell and/or B cell progenitor into one or more of a memory B cell and a plasma cell. In particular, the inventors discovered that IL-21 induces differentiation of human B cells into plasma cells and memory B cells (see, for instance, Example 4 of the specification). Prior to

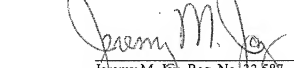
the inventors' discovery, one of ordinary skill in the art would not have recognized that contacting an isolated population of mature B cells and/or B cell progenitors with IL-21 would induce differentiation of human B cells into plasma cells and memory B cells (see paragraph 5 of the "Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D.").

Conclusion

Considering all of the *Graham* factors together, it is clear that the present invention – as defined by the appealed claims – would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combined disclosures of the Newell and Novak references.

For the foregoing reasons, Appellants respectfully request the reversal of the obviousness rejection of the subject patent application.

Respectfully submitted,



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Date: November 15, 2010

Claims Appendix

1.-4. (Canceled)

5. (Previously Presented) A method for enhancing an immune response in a subject, comprising

a) isolating a population of cells comprising one or more of a mature B cell and a B cell progenitor from the subject;

b) contacting the population of cells comprising one or more of a mature B cell and a B cell progenitor with a composition comprising (i) an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid sequence of SEQ ID NO: 1, wherein the variant comprises the amino acid sequence of SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions, and wherein the variant retains the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor,

wherein the population of cells optionally is contacted with at least one antigen, and wherein the composition induces differentiation of at least one of the mature B cell and the B cell progenitor into one or more of a memory B cell and a plasma cell;

c) isolating or purifying one or more of the memory B cell and the plasma cell; and

d) introducing at least one of the memory B cell and the plasma cell into the subject, thereby enhancing the immune response.

6. (Canceled)

7. (Canceled)

8. (Previously Presented) The method of claim 5, wherein the subject is a human subject.

9. (Canceled)

10. (Previously Presented) The method of claim 5, wherein the population of cells is contacted with at least one composition comprising an antigen.

11. (Original) The method of claim 10, wherein the antigen comprises a viral antigen, a bacterial antigen, or an antigen from a parasite.

12. (Previously Presented) The method of claim 5, wherein the B cell progenitor is an immature B cell.

13.-17. (Canceled)

18. (Previously Presented) A method for treating a subject with a condition comprising a specific deficiency of at least one of memory B cells and plasma cells, comprising

a) isolating a population of cells comprising one or more of a mature B cell and a B cell progenitor from the subject;

b) contacting the population of cells comprising at least one of a mature B cell and a B cell progenitor *ex vivo* with a composition comprising (i) an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid SEQ ID NO: 1, wherein the variant comprises the amino acid sequence of SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions, and wherein the variant retains the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide to the IL-21 receptor,

wherein the population of cells optionally is contacted with at least one antigen, and wherein the composition induces differentiation of at least one B cell into one or more of a memory B cell and a plasma cell;

c) isolating the memory B cell, the plasma cell, or both; and

d) introducing at least one of the memory B cell and the plasma cell into the subject.

19. (Canceled)

20. (Previously Presented) The method of claim 18, wherein the subject is a human subject.

21.-31. (Canceled)

32. (Previously Presented) The method of claim 5, wherein the composition comprises (i) the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1.

33. (Previously Presented) The method of claim 18, wherein the composition comprises (i) the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1.

34. (Previously Presented) The method of claim 5, wherein the composition comprises (ii) the variant of the amino acid sequence of SEQ ID NO: 1, wherein 1-5 amino acids of SEQ ID NO: 1 have been substituted, deleted, or added.

35. (Previously Presented) The method of claim 18, wherein the composition comprises (ii) the variant of the amino acid sequence of SEQ ID NO: 1, wherein 1-5 amino acids of SEQ ID NO: 1 have been substituted, deleted, or added.

Evidence Appendix

"Declaration Under 37 C.F.R. § 1.132 of Warren Leonard, M.D.," which was submitted with the "Reply to Office Action" dated April 29, 2010

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132 OF WARREN J. LEONARD, M.D.

I, Warren J. Leonard, M.D., do hereby declare:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-captioned patent application (referred to herein as "the present invention"), which claims priority to U.S. Provisional Patent Application 60/523,754, filed on November 19, 2003. I am aware of the general knowledge available in the art and of the skill level of the ordinary artisan as it exists today and as it existed at the time U.S. Provisional Patent Application 60/523,754 was filed.

2. I have reviewed the Office Action from the U.S. Patent and Trademark Office (USPTO) dated January 4, 2010 regarding the present invention. I understand that the USPTO has rejected the pending claims of the present invention because the Office believes that the subject matter of the pending claims is obvious in view of the teachings of the Novak reference (U.S. Patent Application Publication 2003/0125524) and the Newell reference (U.S. Patent Application Publication 2003/0138433).

3. The pending claims of the present invention are directed to a method for enhancing an immune response in a subject and a method for treating a subject with a condition comprising a specific deficiency of at least one of memory B cells and plasma cells. The methods comprise (a) isolating a population of cells

comprising one or more of a mature B cell and a B cell progenitor from the subject; (b) contacting the population of cells comprising one or more of a mature B cell and a B cell progenitor with a composition comprising (i) an IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 or (ii) a variant of the amino acid sequence of SEQ ID NO: 1, wherein the variant comprises the amino acid sequence of SEQ ID NO: 1 except for 1-5 amino acid substitutions, deletions, or additions, and wherein the variant retains the ability to bind to the IL-21 receptor and produce a physiological effect produced by binding of the IL-21 polypeptide comprising the amino acid sequence of SEQ ID NO: 1 to the IL-21 receptor, wherein the population of cells optionally is contacted with at least one antigen, and wherein the composition induces differentiation of at least one of the mature B cell and the B cell progenitor into one or more of a memory B cell and a plasma cell; (c) isolating or purifying one or more of the memory B cell and the plasma cell; and (d) introducing at least one of the memory B cell and the plasma cell into the subject, thereby enhancing the immune response.

4. I and my fellow co-inventors discovered that contacting a population of cells comprising one or more of a mature B cell and a B cell progenitor with a composition comprising IL-21 induces differentiation of the mature B cell and/or B cell progenitor into one or more of a memory B cell and a plasma cell. In particular, we discovered that IL-21 induces differentiation of human B cells into plasma cells and memory B cells.

5. In my opinion, prior to our discovery, an ordinary artisan would not have recognized that contacting an isolated population of mature B cells and/or B cell progenitors with IL-21 would induce differentiation of human B cells into plasma cells and memory B cells.

6. The Novak reference discloses the characterization of zalpha11 ligand, which is also known as IL-21.

7. The Novak reference generally mentions that "[p]roteins of the present invention are useful for stimulating proliferation, activation, differentiation and/or induction or inhibition of specialized cell function of cells of the involved homeostasis of the hematopoiesis and immune function," wherein hematopoietic lineages include, but are not limited to, T cells, B cells, NK cells, dendritic cells, monocytes, macrophages, and epithelial cells (see paragraph [0125] of the Novak

reference). However, the Novak reference does not correlate stimulation of proliferation, activation, differentiation and/or induction or inhibition with the particular cell types. In other words, the Novak reference lists various functions (i.e., stimulating proliferation, activation, differentiation, induction, and inhibition) and various cell types (T cells, B cells, NK cells, dendritic cells, monocytes, machrophages, and epithelial cells), but does not describe the relationship between the particular function and the particular cell type.

8. The Novak reference teaches that zalpha11 ligand (IL-21) stimulates the proliferation of B cells (i.e., increases the population of undifferentiated B cells) in response to activating stimuli (see Example 44 of the Novak reference). However, the Novak reference does not provide any specific teaching or evidence that contacting IL-21 with a population of mature B cells and/or B cell progenitors results in the differentiation of the mature B cells and/or B cell progenitors into memory B cells and/or plasma cells.

9. The Newell reference merely discloses that a primary encounter with an antigen can stimulate specific B cells to differentiate into cells that produce antibody at a high rate (plasma cells) and populations of memory cells (see paragraph [0010] of the Newell reference). The Newell reference does not disclose IL-21, let alone that contacting IL-21 with a population of mature B cells and/or B cell progenitors results in the differentiation of the mature B cells and/or B cell progenitors into memory B cells and/or plasma cells.

10. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 4/27/2010

Warren J. Leonard, M.D.